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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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Thomas J. Kowalski, Esq.
c/o FROMMER LAWRENC & HAUG LLP
745 Fifth Avenue
New York, NY 10151

EXAMINER	
MAKAR, KIMBERLY A	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/624,317	KOROKHOV ET AL.	
	Examiner	Art Unit	
	Kimberly A. Makar, Ph.D.	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 August 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3,5,7-10,13,15-18,21 and 22* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3,5,7-10,13,15-18,21 and 22* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. In the previous office action claims 1, 3, 5, 7-8, 10 and 13 were rejected under 35 U.S.C. 112, second paragraph. Claims 1, 3, 5, 7-10, 12-13 and 15-18 were rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. Claims 9-10, 12-13 and 15-18 were rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement.

2. Any rejection or objection not maintained in this office action is withdrawn.

3. The following rejection is necessitated by applicant's amendments dated 08/15/07. In the amendments, applicant has clarified the construction of the recombinant adenovirus vector and fusion protein, thereby removing the necessity of the 112 2nd rejection of claims 1,3,5,7-8, 10 and 13 required by the previous examiner which prevented the application of prior art. The newly amended claims, as clarified, render the claims in a condition such that the new examiner believes are subject art rejections.

Claim Rejections - 35 USC § 112

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 9-10, 12-13 and 15-18 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claims contain subject

matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This rejection is maintained although modified to encompass amendments to claims, for reasons of record, repeated and modified herein.

6. The claims are drawn to an antibody-targeted recombinant adenoviral vector complex comprising (i) a gene encoding a heterologous protein; (ii) a wild-type Ad5 fiber protein comprising an immunoglobulin-binding domain of Staphylococcus aureus Protein A, wherein said immunoglobulin-binding domain is a C Domain of Staphylococcus aureus Protein A, and wherein said immunoglobulin-binding domain is inserted at the carboxy terminus of said fiber; and (iii) a gene encoding a fusion protein, wherein the fusion protein comprises (a) comprising a targeting ligand selected from the group consisting of CD40 ligand and a single chain fragment (scFv) of anti-human CD40 antibody and (b) an immunoglobulin Fc domain. The claims encompass any recombinant adenovirus vector complex, comprising a wild-type Ad5 fiber protein comprising an immunoglobulin-binding domain of Staphylococcus aureus Protein A, wherein said immunoglobulin-binding domain is a C Domain of Staphylococcus aureus Protein A, and wherein said immunoglobulin-binding domain is inserted at the carboxy terminus of said fiber; *and/or a gene encoding any fusion protein comprising any immunoglobulin Fc domain and any CD40 ligand or single chain fragment (scFv) of anti-human CD40 antibody.* The single chain fragment (scFV) of an anti-human CD

antibody reads on *any* fragment of an anti-human CD40 antibody that is encoded on that fusion protein.

7. Even if one accepts that the specification teaches in general terms how to make a very small subgroup of vectors with one or two examples of a modified fiber protein comprising an immunoglobulin-binding domain, a gene encoding a Fc-ligand fusion protein, and a heterologous gene, the specification does not describe how to make any adenoviral vector comprising such components such that the virion is capable of being assembled properly and thus propagated.

8. *Vas-Cath Inc. v. Mahurkar*, 19USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, whatever is now claimed." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116).

9. The instant claims, construed as discussed herein above, embrace an recombinant antibody targeted adenovirus comprising an modified fiber protein encompassing a C domain IGG region, and a fusion protein comprising a CD40 ligand single chain antibody fragment domain and a Fc domain, wherein the structural characteristics of the claimed fusion protein are essentially unlimited.

10. The Guidelines for Written Description state "The claimed invention as a whole may not be adequately described if the claims require an essential or critical feature which is not adequately described in the specification and which is not conventional in

the art" (*Federal Register*/ Vol. 66, No. 4/Friday, January 5, 2001/Notices, column 1, page 1105). The Guidelines further state, "[t]he claim as a whole, including all limitations found in the preamble, the transitional phrase, and the body of the claim, must be sufficiently supported to satisfy the written description requirement" (at page 1105, center column, third full paragraph). An applicant shows possession of the claimed invention by describing the claimed invention with all of its limitations. *Lockwood v. American Airlines Inc.* (CA FC) 41 USPQ2d 1961 (at 1966).

11. The Guidelines further state: "when there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus" (*Federal Register*, Vol. 66, No. 4, Column 3, page 1106). "The written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice..., reduction to drawings..., or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus" (MPEP §2163(3)(a)(ii)).

The Guidelines further state, "[s]atisfactory disclosure of a 'representative number' depends on whether one of skill in the art would recognize that the applicant was in possession of the necessary common attributes or features of the genus in view of the species disclosed" (Id. at 1106, column 3).

12. In the instant case, the application discloses methods of producing a fusion protein comprising a CD40 antibody or a CD40 single chain antibody, but does not disclose *any* fragments of a single chain antibody which have or retain any function. Claims 1, 9, and 21 are broad and read on any fragment sequence of a single chain antibody of anti-human CD40 antibodies. There is no requirement that these fragments retain the ability to bind CD40, or have any other function. Thus these species are not representative of the broad genus claimed because they clearly do not convey the necessary common attributes or features of essentially a nucleic acid having any structure-function relationship.

13. The disclosure does not teach what segments of a single chain antibody is required for the invention. In fact, the disclosure only uses what is assumably the full length single chain antibody for anti-human CD40 in their examples. There is no evidence that *any* fragment of the full-length sequences are sufficient to define a genus of any nucleic acid as presently claimed. Therefore, the application also fails to provide the relevant identifying characteristics of the claimed invention.

14. An adequate written description of a method and composition utilizing DNA requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it; what is required is a description of the DNA itself. It is not sufficient to define DNA solely by its principal biological property (i.e., it is capable of anti-repressor activity) because disclosure of no more than that, as in the instant case, is simply a wish to know the identity of any DNA with that biological property. Also, naming a type of material generically known to exist, in the absence of knowledge as to

what that material consists of, is not a description of that material. Thus, claiming a methodology or composition in which all DNA's that achieve a result without defining what means will do is not in compliance with the description requirement. Rather, it is an attempt to preempt the future before it has arrived. (See *Fiers v. Revel*, 25 USPQ2d 1601 (CA FC 1993) and *Regents of the Univ. Calif. v. Eli Lilly & Co.*, 43 USPQ2d 1398 (CA FC, 1997)).

15. Given the very large genus of nucleic acid molecules encompassed by the rejected claims, and given the lack of description provided by the applicant within the specification with regard to the sequences capable of targeting a recombinant adenoviral vector, the skilled artisan would not have been able to envision a sufficient number of specific embodiments that meet the functional limitations of the claims to describe the broadly claimed genus of Ad vectors capable of targeting to a cell surface molecule. Thus, there is no structural/functional basis provided by the instant specification for one of skill in the art to envision those Ad vectors taught in the specification satisfy the broad genus represented in the claims. Therefore, the skilled artisan would have reasonably concluded Applicant was not in possession of the claimed invention for claims 9-10, 113,15-18, and 21-22.

Claim Rejections - 35 USC § 103

16. Claims 1, 3, 5, 9, 10, 13, 15, 21-22 are rejected under 35 U.S.C. 103(a) as being unpatentable over Meruelo et al (US Patent 6,432,699) and Curiel et al (US Patent 6,210,946) and further in view of Ledbetter (US Patent 5,182,368). Claims 1, 3, 5, 9,

10, 13, 15, 21-22 are drawn to an antibody-targeted recombinant adenoviral vector complex comprising (i) a gene encoding a heterologous protein; (ii) a wild-type Ad5 fiber protein comprising an immunoglobulin-binding domain of Staphylococcus aureus Protein A, wherein said immunoglobulin-binding domain is a C Domain of Staphylococcus aureus Protein A, and wherein said immunoglobulin-binding domain is inserted at the carboxy terminus of said fiber; and (iii) a gene encoding a fusion protein, wherein the fusion protein comprises (a) comprising a targeting ligand selected from the group consisting of CD40 ligand and a single chain fragment (scFv) of anti-human CD40 antibody and (b) an immunoglobulin Fc domain. The immunoglobulin-binding domain is inserted into the HI loop or carboxy terminal of the fiber protein, and that fiber protein is a fiber-fibritin chimera.

17. The instant specification fails to define the word "vector." The specification teaches that the vector comprises both the adenoviral genome and a fusion protein. The specification also teaches that a vector complex also comprises both the adenoviral genome and a fusion protein. Thus, for the purposes of prosecution, "vector" is synonymous with "vector complex." The claims read on a system where the fusion protein is encoded by the adenoviral vector *or* provided in trans from an outside source –there is no requirement that the adenoviral genome actually encodes the fusion protein.

18. Using the broadest reasonable interpretation, the phrase, "a gene encoding a fusion protein, wherein the fusion protein comprises (a) comprising a targeting ligand selected from the group consisting of CD40 ligand and a single chain fragment (scFv) of

anti-human CD40 antibody and (b) an immunoglobulin Fc domain" reads on a hybridoma capable of producing a monoclonal antibody specific for CD40, since it would inherently comprise a gene encoding a single chain fragment and an immunoglobulin Fc domain.

19. Meruelo et al (US Patent 6,432,699) teaches viral vectors that can be used to transduce a target cell. The invention "concerns viral vectors that have chimeric envelope proteins and contain the IgG-binding domain of protein A. These vectors when used in conjunction with antibodies targeting a particular cell are particularly useful for gene therapy" (see abstract, see figure 3A (reproduced below))

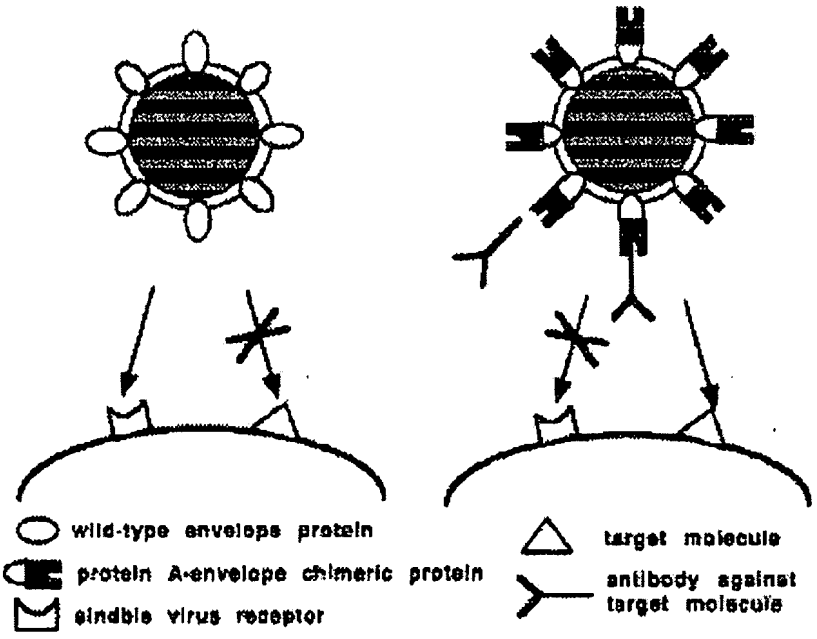

FIG. 3A

20. "The invention concerns viral vectors and their use. Specifically, the invention is concerned with viruses having a protein on the viral particle surface that is a chimeric protein comprising a viral envelop protein and an IgG-binding domain of protein A. Because protein A binds to an Fc region of [an] antibody, these chimeric proteins enable one to use an antibody to target the viral particle to a desired cell to which the antibody binds and not to a cell to which the antibody does not bind" (column 4, lines 64- column 5 line 5).

21. The specificity of the complex is very adaptable to use different targets:

22. The complexes described herein can be provided with a variety of specificities. The application discloses methods of constructing a complex comprising an antibody specific for an acceptor on the target cell so that the vector complex are internalized into the target cell after the vector complex is bound. There are a large number of cell surface antigens suitable. for use as acceptors and for which antibodies are already available. Such structures include, but are not limited to, the class I and class II Major Histocompatibility Antigens; receptors for a variety of cytokines and cell-type specific growth hormones, brain derived neurotrophic factor (BDNF), ciliary neurotrophic factor (CTNF), colony stimulating growth factors, endothelial growth factors, epidermal growth factors, fibroblast growth factors, glially derived neurotrophic factor, glial growth factors, gro-beta/mip 2, hepatocyte growth factor, insulin-like growth factor, interferons (.alpha.-IFN, .beta.-IFN, .gamma.-IFN, consensus IFN), interleukins (IL-1, IL-2, IL-3, IL-4, IL-5, IL-6, IL-7, IL-8, IL-9, IL-10, IL-11, IL-12, IL-13, IL-14), keratinocyte growth factor, leukemia inhibitory factors, macrophage/monocyte chemotactic activating factor, nerve growth factor, neutrophil activating protein 2, platelet derived growth factor, stem cell factor, transforming growth factor, tumor necrosis factors and vascular endothelial growth factor; cell adhesion molecules; transport molecules for metabolites such as amino acids; the antigen receptors of B- and T-lymphocytes; and receptors for lipoproteins. The invention makes possible the specific infection of a cell type by allowing the employ of differentiation antigens as targets for the viral vector complex (column 7, lines 23-52).

23. Meruelo teaches "the viral component of the vector complex can be based on any virus...In addition to ecotropic retroviruses, viruses that can be employed to construct vectors according to this embodiment of the invention include amphotropic retrovirus, herpes virus, adenovirus, and adeno-associated virus (column 8, lines 16-

26). The virus is further modified to comprises a heterologous gene of interest, "that is, the viral complex carries with it a gene of interest encoding a particular antigen. The viral complex will be taken up into the cell and the gene of interest encoding the antigen ...will be expressed in the cellular cytoplasm. By targeting the viral complex to desired cellular target, the antigen will be expressed within the cell of interest (column 8, lines 33-37).

24. Merulo teaches specific embodiments wherein the virus has a modified envelope protein which utilizes the B domain of staphylococcus aureus. He states, "Protein A, a protein derived from Staphylococcus aureus, has a strong affinity fort the Fc region of various mammalian IgGs...Native protein A has five homologous IgG-binding domains (E, D, A, B and C)...The development of retroviral vectors that can bind IgGs (monoclonal antibodies) would have important applications for specific gene delivery" (column 8, line 63 – column 9 line 5).

25. Merulo teaches the potential benefits from the malleability of his system:

26. The use of antibody-antigen interaction as the basis for targeting has a great advantage because a number of monoclonal antibodies have been developed and investigates. Since the protein A portion of the chimeric envelope binds to the Fc domain of the antibody...it allows flexibility with regard to the targeting elements, as any variety of mAbs can be selected...The protein A-envelope chimeric retrovirus displaying mAbs against cell surface antigens should bind preferentially to target cells expressing those antigens, and this may facilitate their infection. Furthermore, in principle, a similar approach may be used with other viral vectors, such as adenovirus and Sindbis virus vectors by inserting the synthetic IgG binding domain (ZZ) or protein A...In conclusion, the novel cell targeting system which utilizes protein A-mAb interaction for virus infection would have broad applications for gene expression studies and therapy" (column 11 lines 44 – column 12 line 4).

27. Thus, Meruelo teaches a highly adaptable recombinant adenovirus comprising a S. aureus protein A IgG-binding domain in the envelope of the adenovirus, that is

targeted to a cells using a antibody for a variety of cell surface markers, wherein the recombinant adenovirus expresses a heterologous gene. Mereulo does not teach that the specific location of the insertion of the S. aureus is in the fiber protein of the adenovirus, that the specific binding domain is the C domain, nor that the antibody is a CD40 antibody.

28. Curiel et al (US Patent 6,210,946) teaches a recombinant adenoviral vector capable ot altering the adenoviral fiber cell-binding protein while maintaining the native trimeric protein biosynthesis profile (see abstract). Curiel teaches that the fiber replacement includes either the entire fiber gene, or portions of the genes; and that the fiber gene incorporates a fibritin gene and a His6 binding domain, and that the adenovirus further comprises a heterologous gene in the genome (column 2, lines 30-65). The introduction of additional targeting ligands can also be incorporated into the fiber gene, either N-terminal or C-terminal including physiological ligands, anti-receptor antibodies and cell specific peptides. Curiel teaches that the adenovirus of his invention expands the utility of recombinant adenoviruses for gene therapy application (column 2, lines 30-32). Curiel has specific embodiments utilizing the Ad5 genome (see examples), and states, "as is well known by those having ordinary skill in this art, the fiber replacement protein will allow the incorporation of various targeting motifs e.g. targeting ligands, targeting antibodies" (column 10 lines 64-57). Curiel does not teach the that adenovirus is targeted to s a cell utilizing a CD40 ligand fusion protein or antibody specific for CD40.

29. Ledbetter et al (US Patent 5,182,368) teaches the identification of a new B-cell receptor, Bp50, ligands for the receptors and antibody fragments for the Bp50 receptor (see abstract). ***Important note: Bp50 is CD40.*** Ledbetter teaches the identification of the CD40 receptor, as well as the development of monoclonal antibodies capable of binding CD40, including the antibody G28.5 (column 6, line 61-63). The G28.5 antibody is produced by hybridomas and only reacts with normal or malignant B-cells or B-cell lines which read on dendritic (see column 8, lines 62- column 9, lines 8, column 11, 1-59). Ledbetter teaches that the G28.5 antibody can be ligated through its Fc domain to new other molecules for targeting molecules to Cd40 expressing cells (Column 7 lines 50 through column 8 lines 17).

30. It would have been obvious to one of skill in the art at the time the invention was made to combine the teachings of Meruelo on a highly adaptable recombinant adenovirus comprising a S. aureus protein A IgG-binding domain in the envelope of the adenovirus, that is targeted to a cells using a antibody for a variety of cell surface markers, wherein the recombinant adenovirus expresses a heterologous gene with the teaching of Curiel et al on an improved recombinant adenovirus utilizing a fiber-fibritin gene that is capable of incorporating binding ligands into the fiber protein capable of maintaining the native trimeric protein biosynthesis profile while altering the tropism of the virus further with Ledbetter et al who provides a targeting CD40 antibody G28.5 capable of directing the adenovirus to CD40 expressing cells by the recombinant adenovirus Protein A IgG domain binding to the Fc domain of G28.5 because Meruelo teaches that his antibody targeting system is malleable, the alteration of tropism of the

virus as taught by Curiel allows for targeting of the adenovirus to alternate ligands, and G28.5 is well known in the art for having multiple homologous IGG binding domains, thereby producing a newly, highly efficient targeting adenovirus, yoking the strengths of the combined references.

31. In respect to Meruelo's specific embodiments directed towards the use of the Protein A IgG binding domains utilizing the B domain, rather than the instantly claimed C domain, Meruelo teaches that Protein A comprises 5 homologous IgG binding domains (see above). It would have been to the skilled artisan to exchange the B domain of Protein A with the C domain of IgG, because both domains are capable of binding the Fc domain of an antibody.

32. All of the claimed elements were known in the prior art, and one skilled in the art could have combined the elements as claimed by known methods with no change in their respective functions, and the combination would have yielded predictable result to one of ordinary skill in the art at the time of the invention (*See KSR International Co. v. Teleflex Inc.,* 82 USPQ2d 1385 (U.S. 2007)). Given the teachings of the prior art and the level of skill of the ordinary skilled artisan at the time the instant invention was made, it must be considered that said ordinary skilled artisan would have had reasonable expectation of success in practicing the claimed invention.

33. Claims 1, 3, 5, 7, 9, 10, 13, 16, 18 and 21 are rejected under 35 U.S.C. 103(a) as being unpatentable over Meruelo et al (US Patent 6,432,699) and Curiel et al (US Patent 6,210,946) and further in view of Tripp et al (US2003/0021808) and Tillman et al (Adenoviral Vector Targeted to CD40 Enhance the Efficacy of Dendritic Cell-based

Vaccination against Human Papillomavirus 16-induced Tumor Cells in a Murine Model. Cancer Research, 60:5456-5463) (listed in applicant's IDS 09/02/04). Claims 1, 3, 5, 7, 9, 10, 13, 16, 18 and 21 are drawn to an antibody-targeted recombinant adenoviral vector complex comprising (i) a gene encoding a heterologous protein; (ii) a wild-type Ad5 fiber protein comprising an immunoglobulin-binding domain of Staphylococcus aureus Protein A, wherein said immunoglobulin-binding domain is a C Domain of Staphylococcus aureus Protein A, and wherein said immunoglobulin-binding domain is inserted at the carboxy terminus of said fiber; and (iii) a gene encoding a fusion protein, wherein the fusion protein comprises (a) comprising a targeting ligand selected from the group consisting of CD40 ligand and a single chain fragment (scFv) of anti-human CD40 antibody and (b) an immunoglobulin Fc domain. The immunoglobulin-binding domain is inserted into the HI loop or carboxy terminal of the fiber protein, and that fiber protein is a fiber-fibritin chimera. The adenoviral vector is further limited wherein the gene encoding the heterologous protein encodes a tumor associated antigen and said fusion protein are operably linked to a dendritic cell-specific promoter.

34. The instant specification does not define "dendritic cell specific promoter." The instant specification does not provide any examples of a "dendritic specific promoter". Thus for the purposes of prosecution, any promoter capable of driving expression in dendritic cells fulfills this limitation.

35. The instant specification fails to define the word "vector." The specification teaches that the vector comprises both the adenoviral genome and a fusion protein. The specification also teaches that a vector complex also comprises both the adenoviral

genome and a fusion protein. Thus, for the purposes of prosecution, "vector" is synonymous with "vector complex." The claims read on a system where the fusion protein is encoded by the adenoviral vector *or* provided in trans from an outside source –there is no requirement that the adenoviral genome actually encodes the fusion protein.

36. The instant rejection is based on the alternate reading of the claims wherein the gene encoding the CD40 ligand fusion protein is encoded on the adenovirus vector.

37. Meruelo et al (US Patent 6,432,699) teaches viral vectors that can be used to transduce a target cell. The invention "concerns viral vectors that have chimeric envelope proteins and contain the IgG-binding domain of protein A. These vectors when used in conjunction with antibodies targeting a particular cell are particularly useful for gene therapy" (see abstract, see figure 3A (reproduced below))

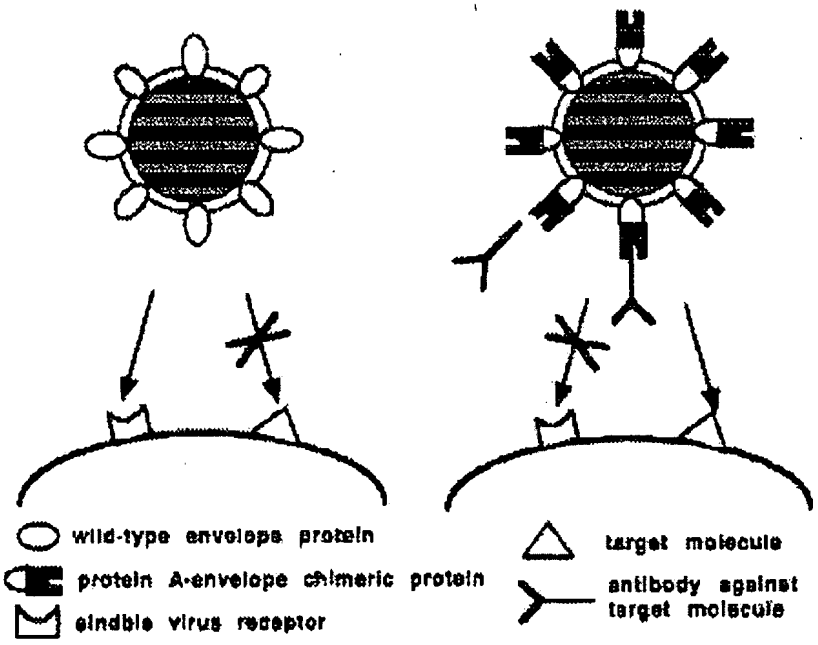

FIG. 3A

38. "The invention concerns viral vectors and their use. Specifically, the invention is concerned with viruses having a protein on the viral particle surface that is a chimeric protein comprising a viral envelop protein and an IgG-binding domain of protein A. Because protein A binds to an Fc region of [an] antibody, these chimeric proteins enable one to use an antibody to target the viral particle to a desired cell to which the antibody binds and not to a cell to which the antibody does not bind" (column 4, lines 64- column 5 line 5).

39. The specificity of the complex is very adaptable to use different targets:

40. The complexes described herein can be provided with a variety of specificities. The application discloses methods of constructing a complex comprising an antibody specific for an acceptor on the target cell so that the vector complex are internalized into the target cell after the vector complex is bound. There are a large number of cell

surface antigens suitable. for use as acceptors and for which antibodies are already available. Such structures include, but are not limited to, the class I and class II Major Histocompatibility Antigens; receptors for a variety of cytokines and cell-type specific growth hormones, brain derived neurotrophic factor (BDNF), ciliary neurotrophic factor (CTNF), colony stimulating growth factors, endothelial growth factors, epidermal growth factors, fibroblast growth factors, glially derived neurotrophic factor, glial growth factors, gro-beta/mip 2, hepatocyte growth factor, insulin-like growth factor, interferons (.alpha.-IFN, .beta.-IFN, .gamma.-IFN, consensus IFN), interleukins (IL-1, IL-2, IL-3, IL-4, IL-5, IL-6, IL-7, IL-8, IL-9, IL-10, IL-11, IL-12, IL-13, IL-14), keratinocyte growth factor, leukemia inhibitory factors, macrophage/monocyte chemotactic activating factor, nerve growth factor, neutrophil activating protein 2, platelet derived growth factor, stem cell factor, transforming growth factor, tumor necrosis factors and vascular endothelial growth factor; cell adhesion molecules; transport molecules for metabolites such as amino acids; the antigen receptors of B- and T-lymphocytes; and receptors for lipoproteins. The invention makes possible the specific infection of a cell type by allowing the employ of differentiation antigens as targets for the viral vector complex (column 7, lines 23-52).

41. Meruelo teaches "the viral component of the vector complex can be based on any virus...In addition to ecotropic retroviruses, viruses that can be employed to construct vectors according to this embodiment of the invention include amphotropic retrovirus, herpes virus, adenovirus, and adeno-associated virus (column 8, lines 16-26). The virus is further modified to comprises a heterologous gene of interest, "that is, the viral complex carries with it a gene of interest encoding a particular antigen. The viral complex will be taken up into the cell and the gene of interest encoding the antigen ...will be expressed in the cellular cytoplasm. By targeting the viral complex to desired cellular target, the antigen will be expressed within the cell of interest (column 8, lines 33-37).

42. Merulo teaches specific embodiments wherein the virus has a modified envelope protein which utilizes the B domain of staphylococcus aureus. He states, "Protein A, a protein derived from Staphylococcus aureus, has a strong affinity fort the Fc region of various mammalian IgGs...Native protein A has five homologous IgG-binding domains

(E, D, A, B and C)...The development of retroviral vectors that can bind IgGs (monoclonal antibodies) would have important applications for specific gene delivery" (column 8, line 63 – column 9 line 5).

43. Merulo teaches the potential benefits from the malleability of his system:

44. The use of antibody-antigen interaction as the basis for targeting has a great advantage because a number of monoclonal antibodies have been developed and investigates. Since the protein A portion of the chimeric envelope binds to the Fc domain of the antibody...it allows flexibility with regard to the targeting elements, as any variety of mAbs can be selected...The protein A-envelope chimeric retrovirus displaying mAbs against cell surface antigens should bind preferentially to target cells expressing those antigens, and this may facilitate their infection. Furthermore, in principle, a similar approach may be used with other viral vectors, such as adenovirus and Sindbis virus vectors by inserting the synthetic IgG binding domain (ZZ) or protein A...In conclusion, the novel cell targeting system which utilizes protein A-mAb interaction for virus infection would have broad applications for gene expression studies and therapy" (column 11 lines 44 – column 12 line 4).

45. Thus, Meruelo teaches a highly adaptable recombinant adenovirus comprising a S. aureus protein A IgG-binding domain in the envelope of the adenovirus, that is targeted to a cells using a antibody for a variety of cell surface markers, wherein the recombinant adenovirus expresses a heterologous gene that is an antigen. Mereulo does not teach that the specific location of the insertion of the S. aureus is in the fiber protein of the adenovirus, that the specific binding domain is the C domain, that the antibody is a CD40 antibody that is encoded on the adenovirus, that the antigen encoded by the adenovirus is a tumor associated antigen, nor that the CD40 fusion protein nor that the two genes are encoded by a dendritic cell specific promoter.

46. Curiel et al (US Patent 6,210,946) teaches a recombinant adenoviral vector capable to altering the adenoviral fiber cell-binding protein while maintaining the native trimeric protein biosynthesis profile (see abstract). Curiel teaches that the fiber

replacement includes either the entire fiber gene, or portions of the genes; and that the fiber gene incorporates a fibritin gene and a His6 binding domain, and that the adenovirus further comprises a heterologous gene in the genome (column 2, lines 30-65). The introduction of additional targeting ligands can also be incorporated into the fiber gene, either N-terminal or C-terminal including physiological ligands, anti-receptor antibodies and cell specific peptides. Curiel teaches that the adenovirus of his invention expands the utility of recombinant adenoviruses for gene therapy application (column 2, lines 30-32). Curiel has specific embodiments utilizing the Ad5 genome (see examples), and states, "as is well known by those having ordinary skill in this art, the fiber replacement protein will allow the incorporation of various targeting motifs e.g. targeting ligands, targeting antibodies" (column 10 lines 64-57). Thus Curiel does teach that the adenovirus can encode a targeting ligand as part of the fiber gene, and a secondary gene. Curiel does not teach the that adenovirus is targeted to as a cell utilizing a CD40 ligand fusion protein or antibody specific for CD40, that the antigen encoded by the adenovirus is a tumor associated antigen, nor that the CD40 fusion protein nor that the two genes are encoded by a dendritic cell specific promoter.

47. Tripp et al teaches that a CD40 ligand fusion protein can be used as adjuvants with vaccinations. Tripp teaches that a CD40 ligand fusion protein comprises "any portion (i.e. fragment) of CD40L, with or without modification, or a modified full length CD40L...attaches to one or more fusion segments" (page 5, paragraph 0034). Suitable fusion segments include immunoglobulin domains or Fc domains (paragraph 0037). Tripp further teaches that a CD40 ligand/Fc fusion protein is known in the art (paragraph

0038). Tripp further teaches that the CD40L fusion protein can be expressed from an adenovirus (paragraph 0020, 0024). Tripp does not teach that the adenovirus is targeted to as a cell utilizing a CD40 ligand fusion protein or antibody specific for CD40, that the antigen encoded by the adenovirus is a tumor associated antigen, nor that the CD40 fusion protein nor that the two genes are encoded by a dendritic cell specific promoter.

48. Tillman et al teaches a CD40 antibody targeted adenovirus is capable of transducing dendritic cells, and that the adenovirus encodes a E7 antigen (see abstract, and page 5456). Thus Tillman teaches an adenovirus capable of dendritic cell specificity by expressing a tumor associated antigen from a CD40 targeted adenovirus, thus this reads on a heterologous gene operably linked to the dendritic cell specific promoter. Additionally, Tillman teaches "we propose to combine this targeting approach with DC-restricted transcriptional regulation to minimize ectopic expression" (page 5462). Tillman further teaches, "Ad targeted to CD40 represents a high-0efficiency, DC-potentiating gene delivery strategy that enhances the efficacy of DC-based immunotherapy strategies in an antigen-specific manner" (page 5462).

49. It would have been obvious to one of skill in the art at the time the invention was made to combine the teachings of Meruelo on a highly adaptable recombinant adenovirus comprising a S. aureus protein A IgG-binding domain in the envelope of the adenovirus, that is targeted to a cell using a antibody for a variety of cell surface markers, wherein the recombinant adenovirus expresses a heterologous gene with the teaching of Curiel et al on an improved recombinant adenovirus utilizing a fiber-fibritin

gene that is capable of incorporating binding ligands into the fiber protein capable of maintaining the native trimeric protein biosynthesis profile while altering the tropism of the virus further with Tripp who provides a targeting CD40 ligand/Fc fusion protein expressed by an adenovirus further with the teaching of Tillman et al on a CD40 targeted adenovirus comprising a tumor associated antigen capable of directing the adenovirus to CD40 expressing dendritic cells thus utilizing a dendritic cell specific promoter operably linked to a heterologous protein because Meruelo teaches his method is very malleable and can target his adenovirus to any cell type; both Meruelo and Curiel teach that the adenoviruses of their invention are capable of expressing more than one heterologous gene, thus it would be obvious to make one of those genes the CD40 ligand fusion protein taught by Tripp. By adding the CD40L/Fc fusion protein to the genome of the adenovirus, one would be able to create the targeting component concurrently with the adenovirus, thereby obviating the step of having to mix the targeting CD40 ligand and adenovirus, steps required by both Meruelo and Tillman in their CD40 targeted adenoviruses. By targeting and expressing the tumor associated antigen in dendritic cells, the CD40 targeted adenovirus acts as an adjuvant thereby propagating an immune response of the therapeutic antigenic gene, as taught by Tripp.

50. In respect to Meruelo's specific embodiments directed towards the use of the Protein A IgG binding domains utilizing the B domain, rather than the instantly claimed C domain, Meruelo teaches that Protein A comprises 5 homologous IgG binding domains (see above). It would have been obvious to the skilled artisan to exchange the

B domain of Protein A with the C domain of IgG, as both domains are capable of binding the Fc domain of an antibody.

51. All of the claimed elements were known in the prior art, and one skilled in the art could have combined the elements as claimed by known methods with no change in their respective functions, and the combination would have yielded predictable result to one of ordinary skill in the art at the time of the invention (*See KSR International Co. v. Teleflex Inc.*, 82 USPQ2d 1385 (U.S. 2007)). Given the teachings of the prior art and the level of skill of the ordinary skilled artisan at the time the instant invention was made, it must be considered that said ordinary skilled artisan would have had reasonable expectation of success in practicing the claimed invention.

52. Claims 8 and 17 are rejected under 35 U.S.C. 103(a) as being unpatentable over Meruelo et al (US Patent 6,432,699) and Curiel et al (US Patent 6,210,946) and further in view of Tripp et al (US2003/0021808) and Tillman et al (Adenoviral Vector Targeted to CD40 Enhance the Efficacy of Dendritic Cell-based Vaccination against Human Papillomavirus 16-induced Tumor Cells in a Murine Model. Cancer Research, 60:5456-5463) (listed in applicant's IDS) as applied to claim 1 and 9 above, further in view of Haynes et al (US patent publication 2003/0162733). Claims 8 and 17 are drawn to an antibody-targeted recombinant adenoviral vector complex comprising (i) a gene encoding a heterologous protein; (ii) a wild-type Ad5 fiber protein comprising an immunoglobulin-binding domain of Staphylococcus aureus Protein A, wherein said immunoglobulin-binding domain is a C Domain of Staphylococcus aureus Protein A, and wherein said immunoglobulin-binding domain is inserted at the carboxy terminus of

said fiber; and (iii) a gene encoding a fusion protein, wherein the fusion protein comprises (a) comprising a targeting ligand selected from the group consisting of CD40 ligand and a single chain fragment (scFv) of anti-human CD40 antibody and (b) an immunoglobulin Fc domain, wherein the heterologous protein is a the tumor associated antigen of prostate specific membrane antigen.

53. Meruelo, Curiel, Tripp and Tillman teach an antibody-targeted recombinant adenoviral vector complex comprising (i) a gene encoding a heterologous protein; (ii) a wild-type Ad5 fiber protein comprising an immunoglobulin-binding domain of Staphylococcus aureus Protein A, wherein said immunoglobulin-binding domain is a C Domain of Staphylococcus aureus Protein A, and wherein said immunoglobulin-binding domain is inserted at the carboxy terminus of said fiber; and (iii) a gene encoding a fusion protein, wherein the fusion protein comprises (a) comprising a targeting ligand selected from the group consisting of CD40 ligand and a single chain fragment (scFv) of anti-human CD40 antibody and (b) an immunoglobulin Fc domain, wherein the heterologous protein is a antigen, and wherein the CD40 ligand fusion protein is encoded on the adenovirus (see above). Tripp teaches that the CD40 fusion protein acts as an antigen, potentiating the effect of a vaccine (see above). Meruelo teaches that the adenovirus expresses a heterologous antigen (see above). Tillman teaches that expressing dendritic cells with a tumor-associated antigen potentiates the effects of a vaccine directed towards that tumor (see abstract and figure 4 of Tillman). However, neither Meruelo, Curiel, Tripp nor Tillman teach that the tumor associated antigen is a prostate specific membrane antigen.

54. Haynes teaches recombinant nucleic acids for enhancing an immune response against an antigen of interest, which includes tumor associated antigens (see abstract, paragraph 0094-0095). Haynes teaches that one such antigen is a prostate membranes specific antigen (Paragraph 0094). Haynes further teaches that the antigen can be encoded on an adenoviral vector (paragraph 0100-0102).

55. It would have been obvious to the skilled artisan to combine the teachings of Meruelo, Curiel, Tripp and Tillman teach an antibody-targeted recombinant adenoviral vector complex expressing an tumor associated antigen capable of potentiating the effect of an vaccine further with the teaching of Haynes that Prostate associated antigen is one tumor associated antigen that can be utilized as a adjuvant to stimulate an immune response, and that it can be expressed by an adenoviral vector because Mereulo teaches that this adenoviruses are malleable and be used to expresses different antigens. All of the claimed elements were known in the prior art, and one skilled in the art could have combined the elements as claimed by known methods with no change in their respective functions, and the combination would have yielded predictable result to one of ordinary skill in the art at the time of the invention (*See KSR International Co. v. Teleflex Inc.,* 82 USPQ2d 1385 (U.S. 2007)). Given the teachings of the prior art and the level of skill of the ordinary skilled artisan at the time the instant invention was made, it must be considered that said ordinary skilled artisan would have had reasonable expectation of success in practicing the claimed invention.

Response to arguments

56. In the response to the office action dated 08/15/07, applicants traverse the rejection of claims 9-10. 12-13 and 15-18 rejected under 112 1st as failing to comply with the written description requirement. Applicant points to the amendments added to the claims which applicant argues renders the rejection moot, and points to example 11 as providing the necessary description for the genus claimed. The examiner respectfully disagrees.. Example 11 is prophetic, and does not address the full scope of the instantly claimed fusion proteins, as identified in the rejection above. Thus the rejection is maintained and modified to address amendments to the claims.

Conclusion

57. No claims are allowed.

58. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of

the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

This office action includes art rejections not previously presented in prosecution. The art rejections provided herein are necessitated by applicant clarifying 112 2nd rejections which rendered the claims indefinite. AS noted above, these rejections have been withdrawn in light of applicant's amendments. As such, the final rejection is proper, and necessitated by applicant's amendments.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Kimberly A. Makar, Ph.D. whose telephone number is 571-272-4139. The examiner can normally be reached on 8AM - 4:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach, Ph.D. can be reached on (571) 272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Kam/11/01/07

DAVID GUZO
PRIMARY EXAMINER